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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/199,874	11/24/1998	GINO V. SEGRE	00786071005	4165

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EXAMINER	
PAK, MICHAEL D	

ART UNIT	PAPER NUMBER
1646	36

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/199,874	SEGRE ET AL.	
	Examiner	Art Unit	
	Michael Pak	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-43 and 52-73* is/are pending in the application.

4a) Of the above claim(s) *41,52-56,59-62 and 64-70* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40, 42-43, 57-58, 63, 71-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Response to Amendment

1. The amendment filed 27 October 2002 (Paper No. 34) has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Applicant's arguments filed 27 October 2002 (Paper No. 34), have been fully considered but they are not found persuasive.

Election/Restrictions

4. Applicants confirm the election of Group VI without traverse on February 4, 2002 (Paper No. 27). Applicants now traverse the restriction requirement and refer to the interview summary of Paper No. 31 filed 10 October 2002. Applicants argue that claim 40 has been amended to indicate that the preamble is now drawn to a method for identifying a compound that inhibits binding of PTH to a PTH receptor by competitively binding to the PTH receptor. In view of applicant's attempt to clarify the invention with the amendment of claim 40 to be generic linking claim, claims 58, 63 and 71 of Group X will be rejoined which are drawn to a method for identifying a compound by binding human receptor which was the group VI originally elected. Claims 40, 42, 43, 57-58, 63, and 71 and new claims 72-73 are examined.

Applicants assume that upon the Examiner's approval of the amendment to claim 40 that Groups I, VII, IV, VIII, V, IX, VI and X will automatically be recombined. In order to clarify the interview of Paper No. 31 filed 10 October 2002, examiner notes that amendments to the claims which may result in the rejoinder and amendments to the claims which may overcome 35 USC112, second paragraph rejection were discussed but that at no time was allowability discussed nor rejoinder of the other groups without the allowance of the claims in Group VI. It should be noted that rejoinder applies only to claims which depend from or otherwise include all the limitations of the patentable claims – usually a product claim. See MPEP 821.04.

Applicants argue that Group I, IV and X should be recombined into a single group because the applicant is entitled to pursue generic claims and should be restricted to examination of claims reciting the specific PTH receptors only if their generic claims are found to be not allowable. However, it should be noted that the claims are not currently allowable. Applicants argue that there is no undue burden to search all of the groups. However, each sequence of the PTH receptor is structurally distinct and requires a separate search in sequence databases.

The requirement is still deemed proper and is therefore made FINAL.

5. This application contains claims 41, 52-56, 59-62, and 64-70 drawn to an invention nonelected without traverse in Paper No. 27. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

6. Claims 40, 42-43, 57, 58, 63 and 71-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 40, 42-43, 58, 71 and 73 encompass the term "parathyroid hormone receptor" which is ambiguous because it is not clear what is the metes and bounds of the term. The term is not defined in the specification and the claim limitations are drawn to structural limitations which requires an initial structure recited in the claim in order to determine the boundaries of the structural limitation. Claims 42 and 43 are dependent on claim 40. Applicants argue that the term is an art recognized and any skilled practitioner would have known what it meant at the time the priority application was filed. Applicants argue that Lindall et al. (US 4,508,828) understood what the term meant in 1983. However, Lindall et al. discussion of parathyroid hormone receptor is directed to a specific species of receptor found in a specific cell whereas the applicants' term "parathyroid hormone receptor" appears to have many different meanings. Page 36 of the specification provide several meaning of the term parathyroid receptor which can be the specific species, naturally occurring receptor, analog, fragment or amino acid substituted receptor which is not the ordinary and customary meaning disclosed in Lindall et al. It is not clear from the specification what is the metes and bounds of the claimed term.

Claims 42 and 43 recite "naturally occurring" which is ambiguous because the it is not clear what is the metes and bounds of the term "naturally occurring". It is not

clear when the receptor is naturally occurring or not and what is the naturally occurring receptor since depending on the definition of the term there may be several naturally occurring forms. Applicants argue that the claims have been amended to now clearly encompass fragments of non-recombinant proteins as well as polypeptides that are produced recombinantly. However, the claimed term is now even more confusing because it is not clear how a "naturally occurring" can be both be non-recombinant and recombinant receptors. It is not clear what is the metes and bounds of a receptor that is naturally occurring and non-naturally occurring. Claims 42 and 43 is dependent on claim 40 thus claim 40 encompasses the term. Claim 57 is dependent on claim 40. Claims 58, 71 and 73 are written generically in the similar manner as claim 40 and thus encompass the term as well.

Claims 40, 42-43, 57, 58, 63 and 71-73 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps do not fulfill the preamble stated purpose of identifying a compound that inhibits binding of a parathyroid hormone to a parathyroid hormone receptor. The method step set forth for competition while identifying a compound which may compete does not identify a compound which inhibits. Competitive binding and inhibition binding have a separate meaning in the art. For example in any binding methods the determination of non-specific binding and determination of specific binding is important because the method assays are in an equilibrium. In the equilibrium if the control assay and the compound testing assay have different receptor concentration or ligand concentration or compound

concentration then the specific binding cannot be determined to be competitive or inhibitory. Furthermore, if the test compound is a protease while it modulates competitive binding is not inhibiting binding since the effect is not related to the affinity of the receptor for ligand or the test compound. A relationship between the specific binding of the competitive binding has to be established with the inhibition of binding.

7. Claims 40, 42-43, 57 and 72-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The newly amended claim 40 and new claim 73 encompass the subgeneric invention which is a combination method of competition and inhibition binding of a test compound. However, the original claim 40 was drawn to competition and the original claims 58 and 71 are drawn to inhibition binding, while the specification does not disclose a method of using a combination of competition and inhibition. Claims 42-43, 57 and 72 are dependent on claim 40.

8. Claims 40, 42-43, 57, 58, 63 and 71-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims encompass a polypeptide variant PTH receptor which is naturally occurring but not disclosed in the specification nor to one of skilled in the art. Claimed polypeptide variants encompass a large genus of receptors which are alleles or variants whose structure has yet to be identified sufficiently to determine whether it functions as a PTH receptor because the structure of the variant receptor which is functional is not known and cannot be envisioned. One of skilled in the art cannot envision the sequence which has not been identified. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian when only the rat protein sequence was disclosed did not have written description in the specification.

Applicants argue that the amendment to claim 40 with regard to "naturally occurring" term which was also discussed above with regard to 35 USC 112, second paragraph, now unambiguously cover both polypeptides extracted from natural tissues and those produced by other means. However, as discussed above it is not clear what is the metes and bounds of a receptor that is naturally occurring and non-naturally occurring. The large genus of molecules which encompass the term is not adequately described in the specification.

Applicants argue that the disclosure of specification provides sufficient variety of species to reflect the variation in the full genus claimed. However, the claims are drawn to receptors without structure and variants which cannot be envisioned from the

disclosed species in the specification. *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* held that a generic claim to human or mammalian or vertebrate receptor when only the rat protein sequence was disclosed did not have written description in the specification. The present claims encompass receptors which are broader than the genus claimed in *University of California v. Eli Lilly and Co. (CAFC) 43 USPQ2d 1398* because naturally occurring variants cannot be predicted. Adequate written description of a variant that possesses the additional characteristic of being naturally occurring requires explicit identification of the strucutural difference between the claimed naturally occurring variant and the reference gene sequence and a non-naturally occurring variant.

9. Claims 40, 42-43, 57, 58, 63 and 71-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of using the receptor which comprises the structural domain which binds the PTH, does not enable a method of using a PTH receptor which comprises any six amino acids to any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims encompass a polypeptide fragments and variants of PTH receptor which comprise at least six amino acids. However, the specification does not teach how to use fragments and variants of PTH receptor which does not bind ligands. G-protein binding receptors have a binding domain comprising the hydrophobic pocket created by all seven of the transmembrane region. A fragment of the G-protein binding receptor

which is truncated in the middle of the hydrophobic pocket or a fragment which does not allow the proper folding of the hydrophobic pocket would not be expected to function since the ligand could not interact with the pocket necessary for intracellular signal transduction function. Furthermore, the state of the art is such that one skilled in the art cannot predict the outcome of changes to protein structure using the primary amino acid structure as the predictor. Thus, one skilled in the art cannot use the primary amino acid sequence of the PTH receptor alone to predict the tertiary structure of the polypeptide which would be required to determine ligand binding function, and proper folding of PTH receptor polypeptide variant with large number of amino acid substitutions. No working example nor guidance are provided to determine whether a change in the hydrophobic ligand binding pocket for PTH polypeptide fragment or variant could bind a ligand. No working example or guidance is provided to use polypeptide without binding function. Thus, such fragments encompass a genus with a large number of species which are not functional. In view of the extent and the unpredictability of the experimentation required to practice the invention as claimed, one skilled in the art could not make the invention without undue experimentation.

Applicants argue that with the detailed information regarding binding of the receptor in the specification, a skilled practitioner would know the structure of any PTH receptor and could easily determine which fragments bind to PTH through routine and predictable experimentation. However, the working example is only with the full length species and claimed invention encompasses a large genus of variant receptors for which it is not predictable to determine whether the receptor binds the PTH and for

which a large number of the claimed genus are variants which are not functional. For example a fragment which is 6 amino acid in length along any of the species sequence does not include the whole ligand binding domain which is unpredictably folded in the tertiary structure of the seven transmembrane domain as well as the extracellular and intracellular domains. One skilled in the art cannot take the primary amino acid sequence to predict the functionality of a 6 amino acid fragments or even 7-90 amino acid fragments which have function and bind and even much less any with substituted amino acids.

Applicants argue that claims functional language excludes polypeptides that are unable to bind parathyroid hormone. However, one skilled in the art could not predictably determine the function of the large number of claimed genus of variant receptors. The prediction of the tertiary structure of a polypeptide based on only 6 amino acids in common with the known receptor and which is functional in ligand binding is an unpredictable art. One skilled in the art cannot take the primary amino acid sequence and predictably determine the tertiary structure of the ligand binding domain and much less the ligand interaction with particular atoms of the amino acids in the ligand binding domain. Additionally, general methods regarding varying the structure of proteins and testing for retained activity do not provide adequate guidance for predictably making and using the scope of the instant invention. A method of finding a receptor that meets the claim limitations by screening is not the same as a method of making. The enablement of the claimed genus would require undue experimentation.

Claim R j ctions - 35 USC § 102

10. Claims 58, 63 and 71 are rejected under 35 U.S.C. 102(b) as being anticipated by Lindall et al. (US 4,508,828).

The reason for the rejection has been set forth previously and set forth again below.

Lindall et al. teach the method of identifying a compound which competes with parathyroid hormone and wherein the compound is the peptides PTH analogues (columns 1,2, 9-12). The PTH receptor in human kidney cortical cell culture of Lindall meets the claim limitations because the human PTH receptor in the human cell inherently comprises the part of the amino acid sequences of SEQ ID NO:21 and is processed for loss of N-terminus methionine.

Applicants argue that Lindall et al. does not describe the use of recombinant polypeptide. Claim 40 and its dependent claims have overcome the rejection. However, the rejoined claims 58, 63 and 71 do not recite newly amended claim limitation "recombinant polypeptide".

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Pak, whose telephone number is (703) 305-7038. The examiner can normally be reached on Monday through Friday from 8:30 AM to 2:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Michael D. Pak
Primary Patent Examiner
Art Unit 1646
25 July 2003